

Top 10 Updates to the National STD Treatment Guidelines

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CDC 2006 STD Treatment Guidelines Development

- Evidence-based on 4 outcomes of STD therapy
 - microbiologic cure, clinical cure, prevention of sequelae and prevention of transmission
- Alternative regimens should not be used unless a medical contraindication to a recommended regimens
- Alphabetized unless there is a priority of choice
- Reviewed in April 2005 and published in September 2006
- www.cdc.gov/std/treatment

Top 10 Updates in 2006

1. Prevention recommendations and targeted screening in special populations
2. Expedited partner treatment and re-testing after treatment for CT and GC
3. Diagnostic testing recommendations
 - Use of NAATs for diagnosis of CT and GC
 - Syphilis diagnosis with EIA Syphilis diagnosis with EIA
 - Role of HSV serologic testing
4. Criteria for diagnosing early latent syphilis
5. Role of LP in the clinical management of syphilis

Top 10 Updates in 2006

6. Emerging antimicrobial resistance
 - GC
 - Syphilis
 - Trichomoniasis
7. Age- and risk-based empiric treatment for cervicitis
8. Role of metronidazole in PID Treatment
9. HSV Treatment Approaches
10. LGV emergence in MSM

1. Prevention Issues

- Sexual history taking and risk reduction counseling including the 5 P's
- Condom messages
 - ◆ Might reduce risk of developing PID and risk for transmission of HSV and HPV
 - ◆ Use of condoms with N-9 not recommended
- Patients should be informed about which STDs they are tested for (and which not)
- Emergency contraception should be available
- Non-occupational PEP for HIV prevention as a result of sexual exposure
- Specials population: pregnant women, adolescents, MSM, and WSW
 - ◆ Pap smear screening recommended according to national guidelines for WSW
 - ◆ Trich, BV, HPV and HIV of most concern in WSW

2. Partner Treatment

- Patient referral
- Provider or clinic referral
- Health department referral
- Expedited Partner Treatment (EPT)
 - ◆ Patient-delivered partner therapy (PDPT)
 - ◆ Health department-delivered therapy
 - ◆ Pharmacy-delivered therapy

Chlamydia and Gonorrhea Expedited Partner Treatment

Expedited Partner Treatment (EPT) or Patient Delivered Partner Treatment (PDPT)

- Option for partner management for heterosexual men and women
 - Written materials should accompany medication and specially mention concern about PID in female partners
- First line management is clinical evaluation
- Not recommended in MSM because of concern regarding co-morbidities (e.g., HIV and other STDs)
- CDC has developed separate guidance on EPT/PDPT

Recommendations for Chlamydia and Gonorrhea Re-Testing after Treatment

- Prefer “re-testing” to “re-screening”
- High rates of re-infection after treatment and for GC may confer an elevated risk of PID
- Consider re-testing of females; some experts suggest re-testing of males for CT and consider re-testing of males for GC
- Time frame: 3 months after treatment and for GC whenever seek care within 12 months if did not return at 3 months
- No test of cure except in pregnant women with CT and for GC if treated initially with a fluoroquinolone and symptoms persist or recur after treatment

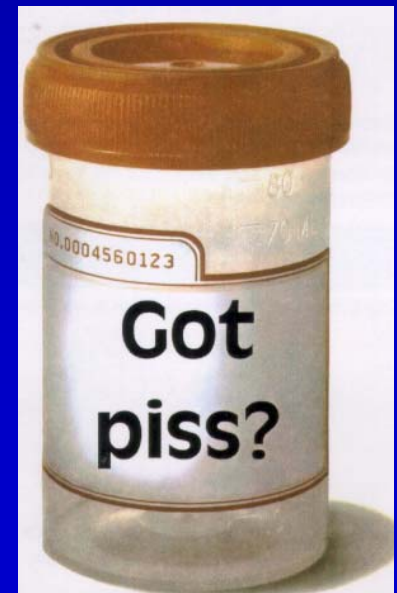
3. Diagnostic Recommendations

Chlamydia/Gonorrhea Diagnostic Tests

- Gram stain only for men
- Culture
- Antigen Detection Tests: EIA, DFA
- Nucleic Acid Non-amplified Detection Tests
 - ❖ GenProbe PACE 2
- Nucleic Acid Amplification Tests (NAATs)
 - ❖ Roche *Amplicor* (PCR)
 - ❖ GenProbe *Aptima* (TMA)
 - ❖ B-D *ProbeTec* (SDA)

Recommend Nucleic Acid Amplification Tests for Detecting Chlamydia and Gonorrhea

- Highest sensitivity
 - ◆ Able to detect up to 40% more CT infections
 - ◆ Less dependent on specimen collection and handling
- Noninvasive
 - ◆ Urine and self-collected vaginal swabs
- Non-clinical settings
 - ◆ Pelvic and genital exams not necessary
 - Clinic intake areas
 - Community based organizations
 - Home testing



Syphilis Diagnostic Tests

- Darkfield/DFA-TP
- PCR
- Non treponemal tests
 - ◆ VDRL/RPR
- Treponemal tests
 - ◆ FTA-abs / TP-PA (MHA-TP)
 - ◆ EIA
 - Captia, Trep-Chek, Trep-Sure, Liaison

Syphilis EIA Treponemal Tests

- ◆ Treponemal tests FDA cleared for clinical use
 - Captia, Trep-Chek, Trep-Sure, Liaison
- ◆ Can be used for screening but if positive then need quantitative reflexive RPR/VDRL for clinical management
- ◆ Both IgM and IgG tests available
 - No clinical value of IgM in adult early syphilis diagnosis
- ◆ Advantages
 - No prozone, low cost, automated, and less lab occupational hazard (pipeting)
- ◆ Disadvantages
 - Studies to compare test performance with TP-PA are needed
 - Sensitivity and Specificity concerns regarding Captia
 - Specificity concerns regarding Trep-Chek

Kaiser Syphilis EIA Screening Algorithm, 2005

- Screen with EIA and repeat positives/equivocals
- If positive x 2, reflexive quantitative RPR/VDRL
- If negative RPR/VDRL, reflexive TP-PA
- Positive predictive value of a positive EIA for syphilis with a negative RPR and TP-PA is low
- Lab reports as unconfirmed positive EIA test which most likely represents a false positive results
- If patient is low risk for syphilis no further follow-up
- If patient is high risk for syphilis, advise to repeat serologic test in one 1 month

Type-Specific* gG-based HSV Serology Tests

- HSV-1 and HSV-2 Immunoblot IgG (Focus Technologies- HerpeSelect)
 - ◆ Sensitivity 97-100%, Specificity 96-97%
- HSV-1 and HSV-2 ELISA IgG (Focus Technologies- HerpeSelect)
 - ◆ Sensitivity 96-100%, Specificity 94-98%
- Captia ELISA HSV-2 (Trinity Biotech)
 - ◆ Sensitivity 90-92%, Specificity 91-98%
- Biokit HSV-2 & SureVue HSV-2 (Biokit & Fisher Scientific) Point of care tests
 - ◆ Sensitivity 93-96%, Specificity 95-98%

GOLD STANDARD: Western Blot (>99% sensitivity and specificity)

** Note: Older non-specific tests are still on the market.*

HSV Screening and Testing Recommendations

- HSV-2 serology tests may be useful in the following situations
 - ◆ Clinical diagnosis without lab confirmation
 - ◆ Patients with a partner with genital HSV
- Some experts recommend serologic tests:
 - ◆ As part of “comprehensive STD evaluation” in high risk individuals
 - multiple partners, HIV-infected, MSM with high HIV risk
 - ◆ In pregnant women with no history of HSV and a partner with history of genital HSV
- Universal screening is not recommended

4. Latent Syphilis Classifications

- No clinical manifestations
 - ◆ Only evidence is positive serologic tests
- Divided into two stages for treatment purposes
 - ◆ Early latent syphilis: <1yr duration
 - ◆ Negative syphilis serology in past year
 - ◆ Known contact to an early case of syphilis
 - ◆ Good history of typical signs/symptoms in past year
 - ◆ (4-fold increase in titers in past year)*
 - ◆ Positive syphilis serology in a person whose only exposure occurred in the previous 12 months
 - ◆ Late latent syphilis: >1yr duration
 - Includes syphilis of unknown duration
 - Clinical management errs on the side of being conservative when information is absent
 - Should this be called Latent syphilis

* Could be treatment failure

5. Neurosyphilis and When to LP?

- Central nervous system invasion occurs early in infection in 30-40% of patients
 - Majority are asymptomatic
- Neurosyphilis can occur at any stage of syphilis
 - Early symptomatic forms (months to a few years)
 - Acute syphilitic meningitis (CN VI, VII, VIII)
 - Meningovascular (stuttering stroke)
 - Late symptomatic forms (> 2 years)
 - General paresis and Tabes dorsalis
- Ocular syphilis
 - Posterior chamber uveitis is typical but retinitis and retinal detachment with CSF inflammation are common

CDC Criteria for CSF Examination

- Neurologic or ophthalmic symptoms/signs
 - Neurologic and ocular complaints in young individuals at risk for syphilis should prompt consideration of syphilis
- Evidence of tertiary disease
- Treatment failure
 - Less than a fourfold decrease in serology titer within 6-12 months after treatment of early syphilis
- HIV infection with late latent or latent of unknown duration
- Some experts recommend a CSF exam in all patients with latent syphilis and an RPR titer $\geq 1:32$ or all HIV-infected patients with CD4 count ≤ 350

Evidence for CSF Examination if RPR $\geq 1:32$ or CD4 count ≤ 350

- One study of 326 patients with syphilis referred for LP because they met the 1993 CDC criteria
 - ◆ *Marra et al, JID 2004; 189:369-76*
 - ◆ 125 with symptoms of syphilitic meningitis or ocular syphilis
 - ◆ 65 met the laboratory case definition of NS
 - Positive CSF VDRL or
 - CSF WBCs > 20 cells/ μ L
- Lab diagnosis of NS was not more common in patients with Sx
- Follow-up of 59 patients after NS treatment found CSF VDRL and WBC abnormalities normalized in “virtually all patients by one year”

Questions Regarding the Recommendation for LP if RPR $\geq 1:32$ or CD4 count ≤ 350 ?

- Who are the patients affected by this recommendation?
 - ◆ HIV negative patients with latent syphilis and RPR $\geq 1:32$
 - ◆ HIV positive patients with early latent and RPR $\geq 1:32$ or CD4 ≤ 350
- How large is this group?
- What is the clinical benefit of treating aSx NS in this group?
 - ◆ The clinical and prognostic significance of these lab abnormalities remain unknown
- What is the cost and potential negative consequences of the recommendation?
 - ◆ e.g.- hospitalization, delay in treatment of infectious cases to schedule LPs which furthers the spread of syphilis in the community
- Why change the LP criteria now based on one study after years of conventional treatment of many patients and very limited number reported adverse events after treatment?

6. Emerging Antimicrobial Resistance

Update to CDC's **Sexually Transmitted Diseases Treatment Guidelines, 2006**: Fluoroquinolones No Longer Recommended for Treatment of Gonococcal Infections

In the United States, gonorrhea is the second most commonly reported notifiable disease, with 339,593 cases documented in 2005 (1). Since 1993, fluoroquinolones (i.e.,

MMWRTM

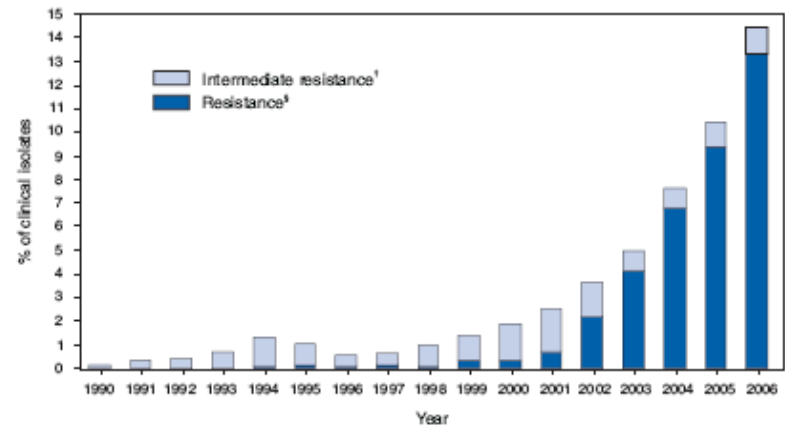
Morbidity and Mortality Weekly Report

Weekly

April 13, 2007 / Vol. 56 / No. 14

CIPRO

FIGURE. Percentage of *Neisseria gonorrhoeae* isolates with intermediate resistance or resistance to ciprofloxacin, by year — Gonococcal Isolate Surveillance Project, United States, 1990–2006*



* Data for 2006 are preliminary (January–June only).

† Demonstrating ciprofloxacin minimum inhibitory concentrations (MICs) of 0.125–0.500 µg/mL.

§ Demonstrating ciprofloxacin MICs of ≥1.0 µg/mL.

Gonorrhea Treatment, 2007

Recommended regimens:

- Ceftriaxone 125 mg IM x 1
- Cefixime 400 mg PO x 1
 - Currently available only as suspension
- ~~■ Ciprofloxacin 500 mg PO x 1~~
- ~~■ Ofloxacin 400 mg PO x 1~~
- ~~■ Levofloxacin 250 mg PO x 1~~

Alternative regimens:

- ★ **Cefpodoxime 400 mg po x 1**
- ★ **Cefuroxime 1 g po x 1**
- Spectinomycin 2 g IM x 1: not available
- Single-dose injectable cephalosporin regimens
- Azithromycin 2 gm PO

Co-treat for chlamydia unless ruled out *with highly sensitive NAAT*

Gonorrhea – Treatment Issues

- Limited options in cephalosporin allergic patients:
 - ◆ Spectinomycin is no longer manufactured
 - ◆ CDC recommends desensitization
 - ◆ Could be a special case to consider azithromycin, but
 - Requires 2 grams; GI tolerance issues
 - Resistance to azithro likely increasing and treatment failures have been seen
 - ◆ If fluoroquinolones are the only option, obtain culture if possible prior to treatment to document FQ sensitivity; if not possible, obtain test-of-cure (3-5 days if culture, 3 weeks if NAAT)

Efficacy Data for Agents with Activity Against GC Infection

Agent, dose, route	Site	Studied	Cured	% Cure (95%CI)
Ceftriaxone 125 IM	SS	442	438	99.1 (98.7, 99.8)
	PH	63	59	93.7 (84.5, 98.2)
Cefixime 400mg PO	SS	344	336	97.7 (96.1, 99.3)
Cefpodoxime 200 PO (*)	SS	284	274	96.5 (94.3, 98.6)
	PH	19	15	78.9 (54.5, 94.0)
Cefpodoxime 400 PO (**)	SS	316	305	96.5 (93.9, 98.2)
	SS §	287	281	97.9 (95.5, 99.2)
	PH	35	26	74.3 (56.7, 87.5)
Cefuroxime 1 gm PO	SS	469	454	96.8 (95.2, 98.4)
	PH	29	16	55.2 (37.1, 73.3)

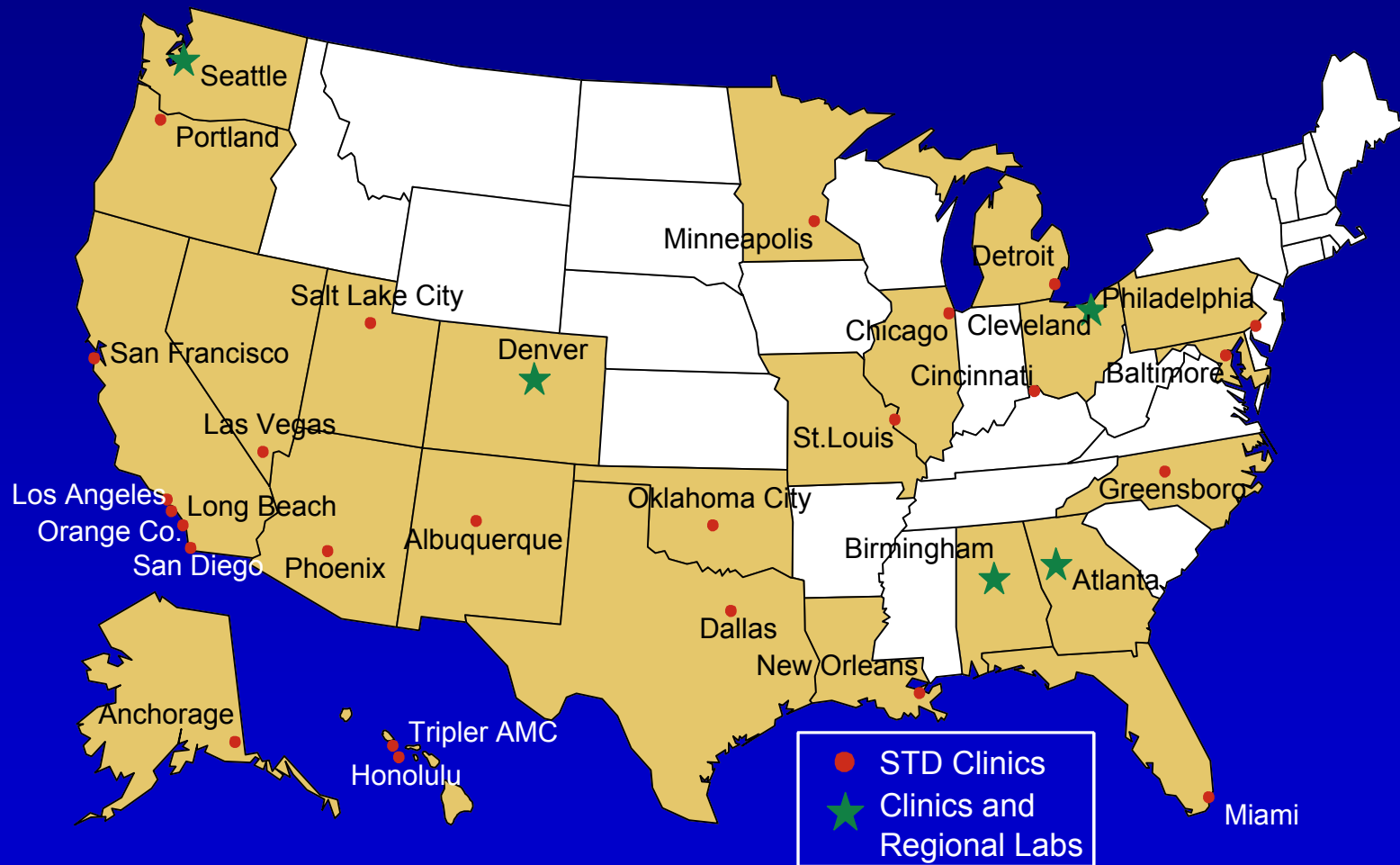
Site: SS - single urogenital or rectal; PH - pharynx; MS - multiple or unspecified. SS § - urogenital, with sex in treatment interval excluded

John Moran, William Levine. CID 1995; 20 (Suppl 1): S47-65

* Novak et al., Antimicrob Agents Chemother 1992; 36: 1764-5

** Hall et al., ISSTD 2007; Abstract P-459

Gonococcal Isolate Surveillance Project (GISP) : United States, 2003



Syphilis Resistant to Azithromycin!



The NEW ENGLAND
JOURNAL of MEDICINE

Macrolide Resistance in *Treponema pallidum* in the United States and Ireland

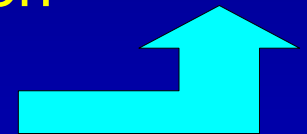
Sheila A. Lukehart, Ph.D., Charmie Godornes, B.S., Barbara J. Molini, M.S.,
Patricia Sonnett, B.S., Susan Hopkins, M.D., Fiona Mulcahy, M.D.,
Joseph Engelman, M.D., Samuel J. Mitchell, M.D., Ph.D., Anne M. Rompalo, M.D.,
Christina M. Marra, M.D., and Jeffrey D. Klausner, M.D., M.P.H.

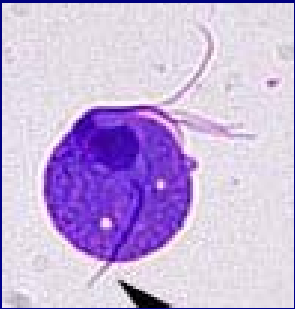
N Engl J Med 2004;351:154-8.

Syphilis Treatment



- Primary, secondary & early latent
 - Benzathine PCN G (L-A) single dose IM 2.4 million units
 - Do not use other PCN formulations!
 - Do not use azithromycin
 - Doxycycline 100 mg PO bid x 14 days (inferior)
 - Ceftriaxone 1 g IV or IM daily x 8-10 days (inferior)
- Late latent or unknown duration
 - Benzathine PCN G IM 2.4 million units weekly x 3 doses (7.2 million u total)
 - Doxycycline 100 mg PO bid x 28 days (inferior)





Trichomoniasis Treatment

Recommended regimen:

- ◆ Metronidazole 2 g PO x 1
- ◆ **Tinidazole 2 g po x 1**

Alternative regimen:

- ◆ Metronidazole 500 mg PO BID x 7d

Recommended regimen in pregnancy:

- ◆ Metronidazole 2 g PO x 1
 - Pregnancy category B and Tinidazole is category C

Discussed Trichomoniasis Treatment Failure Options

- **Re-treat with:** Metronidazole 500 mg po BID x 7 d or **Tinidazole 2 g po x 1**
- **If repeat failure, treat with:** Metronidazole or **Tinidazole 2 g po x 5 d**
- Some experts treat with: **Tinidazole 2-3 g po x 14 d**
- Susceptibility testing: Send isolate to CDC
 - ◆ 707-488-4115 or www.cdc.gov/std for instructions
- Metronidazole-resistant trichomonas:
 - ◆ Tinidazole 500 mg PO QID (or 1 g BID) + 500 mg intravaginal bid x 14 d
 - ◆ Alternatives include paromomycin cream (can cause ulcers), 250 mg q d for 14 d; furazolidone; zinc oxide douche; N-9

Tinidazole: a option for treatment failures

- Second generation 5-nitroimidazole
 - ◆ 92%-100% effectiveness for trichomoniasis
 - ◆ Contraindicated in pregnancy (category C)
- Advantages over Metronidazole
 - Greater tolerability (approx. $\frac{1}{2}$ incidence of nausea, vomiting and other GI side effects)
 - Longer duration of action ($t_{1/2}$ of 12-14 hrs vs 6-7 hrs)
 - Greater in vitro potency against protozoa and anaerobes (lower MICs)
 - Enhanced penetration in genital tissues
 - Effective in metronidazole-resistant trichomoniasis
 - 92% (22/24) cure rate in largest report

7. Cervicitis Management

- Symptoms: nonspecific and insensitive
 - ◆ vaginal discharge
 - ◆ intermenstrual/postcoital bleeding
- Signs: specific, but insensitive
 - ◆ easily induced endocervical bleeding
 - ◆ mucopurulent discharge: swab test
 - ◆ other previously used signs non specific
 - Erythema or elevated # of WBCs
- Inflammation detected on endocervical Gram stain is of limited usefulness in helping to define cervicitis



Diagnostic Evaluation of Cervicitis

- Consolidation of evidence supporting NAAT as preferred diagnostic assays for CT/GC
 - ◆ Accurate in presence of blood or mucopus
- Availability of sensitive, rapid tests for *Trichomonas vaginalis*
 - ◆ Point-of-care Ag-based detection assay (OSOM rapid test, Genzyme;), sens 83.3%, spec 98.8%
 - ◆ Affirm test
- Role of quantifying WBC in vaginal fluid
 - ◆ >5-10 WBC/HPF in vaginal fluid strongly associated with cervical CT/GC, high PPN (particularly in BV)

Johnson
2002,
Marrazzo
2004

Huppert
2005

Geisler 2004,
Hakakha 2002,
Steinhandler 2002

Empiric Therapy of Cervicitis

- Age- and risk-based empiric therapy:
 - ◆ Age < 25, treat for Ct and (usually) GC
 - ◆ Age > 25, treat for Ct based on risk factors and likelihood of follow-up, otherwise await Ct/GC test result
 - ◆ GC treatment should be based on risk, likelihood of follow-up, local (patient group/clinic/neighborhood) prevalence > 5%
- For lower-risk women can try 1 course of antibiotics
 - ◆ Choice of antibiotic unclear
- Evaluate for BV and trichomoniasis; treat if present
- If treatment is deferred, use NAAT results to direct future treatment for CT/GC

8. Pelvic Inflammatory Disease Management

- Newest etiologic agent: *Mycoplasma genitalium*
 - ◆ Pathogenesis unclear
 - ◆ No recommendation for Mg testing
- If no evidence of cervicitis and no WBCs on wet mount the diagnosis of PID is unlikely
- Modify minimal criteria for presumptive treatment:
 - ◆ CMT **OR** uterine tenderness **OR** adnexal tenderness
- Clarify use of metronidazole
 - ◆ Treatment to cover anaerobes should be considered
 - ◆ If BV is present or cannot be ruled out, add metronidazole
- Azithromycin treatment mentioned “outside the box”

With or Without Metronidazole??

- BV associated with PID and other upper tract abnormalities
- Assess for BV
 - ◆ Wet mount or POC; use metronidazole if BV present
 - ◆ If no lab confirmation available, use metronidazole

PID: Oral Treatment Regimens

Oral regimen A:

- ◆ Ofloxacin* 400 mg PO BID** x 14 d *or*
- ◆ Levofloxacin* 500 mg PO QD x 14 d
plus (with or without)
- ◆ Metronidazole 500 mg PO BID x 14 d

*Contraindicated pregnant or nursing women and in CA, if GC documented and flouroquinolone is used need TOC culture

** typographical error in guidelines- not once daily

PID: Oral Treatment Regimens

Continued

Oral regimen B:

- ◆ Ceftriaxone 250 mg IM (or other parenteral 3rd generation cephalosporin) x 1 **or**
- ◆ Cefoxitin 2 g IM *and* probenecid 1 g PO x 1
plus
- ◆ Doxycycline* 100 mg PO BID x 14 d
with or without
- ◆ Metronidazole 500 mg PO BID x 14 d

*Contraindicated pregnant or nursing women

9. HSV Treatment Approaches

■ Initial Infection

- ◆ Treat because may develop severe or prolonged symptoms later

■ Established Infection

- ◆ Suppressive therapy for recurrent HSV
- ◆ Suppressive therapy to reduce transmission
 - Discordant heterosexual couples where the partner has a hx of genital HSV
 - Other possible indications mentioned: Persons with multiple partners including MSM, Persons who are HSV-2 seropositive without a history of genital HSV, and HIV infected individuals
- ◆ Episodic Therapy for recurrent HSV

10. LGV Outbreaks Reported



Morbidity and Mortality Weekly Report

October 29, 2004 / Vol. 53 / No. 42

Lymphogranuloma Venereum Among Men Who Have Sex with Men — Netherlands, 2003–2004

- Netherlands: 92 confirmed cases between 4/03 and 9/04
- Majority with bloody proctitis, mucopurulent anal discharge
- Similar outbreaks in 2004 in Antwerp, Hamburg, Paris, Sweden, and UK
- Recent reports in Canada and U.S.
- Nearly all MSM

Lymphogranuloma Venereum (LGV)

C. trachomatis serovars L1, L2, L3



- Clinical presentation
 - ◆ Lymphadenopathy syndrome: ulcer & inguinal adenopathy (bubo)
 - ◆ Anorectal syndrome: proctitis/proctocolitis
 - Mucoid/hemorrhagic rectal discharge, anal pain, constipation, tenesmus
- Complications from destructive granulomatous process
 - ◆ abscesses with scarring, fistulae, strictures, genital elephantiasis

LGV Management

- LGV has been around for some time
 - ◆ May be asymptomatic
- Clinical presentation typically includes proctocolitis in MSM
 - ◆ Consider GC and HSV in differential
- Diagnosis is primarily by clinical findings/history
 - ◆ Test for rectal CT
 - ◆ Swabs of rectal lesions visualized by anoscopy is better than blind rectal swab
 - ◆ CDC can do molecular testing of suspect rectal swabs/lesions (404-639-2059)
 - ◆ Role of serologic testing is less clear

LGV Proctocolitis:

Serologic Diagnosis

- Microimmunofluorescence (MIF)
 - ◆ species-specific test
 - ◆ titer $\geq 1:256$ is suggestive (arbitrary cut point)
- Complement Fixation (CF)
 - ◆ genus-specific
 - ◆ positive 2 weeks after infection
 - ◆ titer $\geq 1:64$ suggestive of LGV
 - ◆ high background rate of low titer reactors

LGV Proctocolitis:

Treatment Issues

- Presumptive treatment for LGV based on clinical suspicion along with other empiric treatment for proctocolitis: (Ceftriaxone 125 mg IM plus)

Recommended regimen:

- ◆ Doxycycline 100 mg PO BID x 21 days

Alternative regimen:

- ◆ Erythromycin base 500 mg PO QID x 21 days

Likely effective but clinical data lacking:

- ◆ Azithromycin 1 g PO weekly for 3 weeks

- Partners within past 60 days of onset of symptoms need evaluation. If no symptoms, treat with:
Azithromycin 1 g or Doxycycline 100 mg BID x 7 days

STD Resources

California STD/HIV Prevention Training Center

www.stdhivtraining.org

California STD Control Branch

www.dhs.ca.gov/ps/dccdc/STD/stdindex.htm

CDC STD Program

www.cdc.gov/std

California Chlamydia Action Coalition

www.ucsf.edu/castd

Questions ???